REMARKS

Claims 37 and 39 have been amended to overcome the informalities noted by the Office which resulted in a rejection under 35 U.S.C. § 112, paragraph 2. It is believed that these amendments obviate the rejection.

First, applicants very much appreciate the withdrawal of the previous rejections. Their response to the new rejections now outstanding is as follows:

The Rejection Under 35 U.S.C. § 112, Paragraph 2

This basis for rejection has been obviated by amendment. Should the undersigned have missed an occurrence of an ambiguity, a telephone call pointing this out is respectfully requested.

The Art Rejections

Claim 37 was rejected as assertedly unpatentable over Contag (U.S. 5,650,135) in view of Yang, *et al.* (*PNAS* (2000) 97:1206-1211).

Contag, while mentioning green fluorescent protein in passing, clearly demonstrates only the use of luciferase to envision expression controlled by an endogenous promoter. Contag, in fact, teaches away from the use of fluorescent protein as noted in column 9, line 62 to column 10, line 6 stating that autofluorescence such as that of luciferase is preferable to the use of fluorescent proteins which require excitation by external sources, so that background is minimized. Contag also teaches away from fluorescence in the green or blue since these wavelengths are absorbed (column 8, line 35 *et seq.*) As to the passage with regard to "immobilized" subjects, a review of the examples set forth in Contag clearly reveals that the circumstances under which "an image can be constructed in a time short relative to the timescale at which the immobilized subject moves" has not been realized or taught. At best this is wishful thinking.

Applicants appreciate that the Office understands that Contag alone falls far short of suggesting the method of the invention since Yang is cited as showing that the ability to observe fluorescence by whole body imaging in a mammalian laboratory animal would predictably be successful.

Respectfully, Yang does not predict this. Yang is concerned with imaging tumors which have been constructed of cells that are deliberately prepared to express large amounts of fluorescent protein. As noted on page 1209, in order to generate B16F0-GFP tumors, stable high level expression GFP transductants of B16F0-GFP cells are employed, and these are selected for high GFP expression. This is why the tumor cells are bright and easily visualized.

The invention method, on the other hand, relies on expression controlled by endogenous promoters which are not designed to provide high level expression of a single protein in any particular cell. For this reason, it is not predictable that the ability to envision tumors and metastases by whole body imaging using tumor cells that are artificially modified to generate high expression levels of GFP predicts the success of measuring, by the same method, monitoring expression under the control of a promoter of an endogenous gene (or using such measurements in a method to screen for a modulator for expression of such a gene). Whole body fluorescent imaging of tumors artificially altered to ensure high level expression of GFP is vastly different from measuring the comparatively feeble levels of expression that would be engendered by endogenous gene promoters.

For this reason, the combination of Yang with Contag does not render claim 37 obvious.

Claim 39 was rejected as unpatentable over Lin (U.S. 6,380,458) in view of Contag and Yang. This rejection is similar to the previous one except that it employs Lin as teaching creation of genetically modified zebrafish which then could be used to assess the effect of a mutant gene on the

expression of a gene of interest. In other words, Lin is cited for disclosing the elements of administering a mutation-inducing agent to obtain animals with a mutation that may affect expression of a "gene of interest." Applicants do not quarrel with this assessment of Lin, although, of course, as the Examiner kindly recognizes, zebrafish are inapposite to the present invention as they are not opaque organisms like the laboratory mammals required by the claims.

The remainder of the rejection is as applied to claim 37, and these arguments need not be repeated. Because it is clear that Lin in combination with Contag does not suffice alone to render the invention obvious, the addition of the Yang document is required. The Yang document, however, does not fill the gap left by Contag and Lin because it describes the use of whole body imaging for detecting fluorescence in a completely non-analogous situation where high levels of expression in specialized cells are assured.

For this reason, the foregoing rejection may be withdrawn as well.

Claim 37 was rejected as obvious over Contag in view of Tan, *et al.* (U.S. 6,251,384). This basis for rejection is analogous to that of Contag in combination with Yang. Like Yang, Tan discloses production of tumor cells with very high levels of expression of GFP. See, for example, column 8 at lines 11-12, "clone 26 was chosen because of its high intensity GFP fluorescence and stability."

Thus, as was the case with Yang, there is simply no analogy between the ability to observe tumors and metastases using whole body imaging and measuring the expression of an endogenous gene controlling the production of GFP.

Claim 39 was rejected as obvious over Lin in view of Contag and in further view of Tan.

This rejection, too, tracks the rejection over the combination of Lin, Contag and Yang, and may be withdrawn for the same reasons. Tan does not provide a reasonable expectation of success

in measuring endogenous gene expression levels by whole body imaging because there is no capability to ensure high levels of expression as is inevitably the case in both Yang and Tan.

Conclusion

Applicants appreciate that the Yang and Tan documents are added to the previous rejections to provide predictability of success. However, they do not provide such predictability because the conditions for observing tumors designed to have high levels of expression of fluorescent proteins by whole body imaging does not predict or suggest the ability to use whole body imaging to measure expression controlled by endogenous promoters which are not designed to effect high levels of expression of sequences under their control. For this reason, applicants believe claims 37 and 39 are in a position for allowance and passage of these claims to issue is respectfully requested.

Should minor issues remain that could be resolved over the phone, a telephone call to the undersigned is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 312762002710.

Respectfully submitted,

Dated: August 25, 2010 By: / Kate H. Murashige /

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